Advisory Action

Application No.	Applicant(s)
09/341,894	Pl chaczyk et al.
Examiner	**Art Unit**
Peter Brunovskis	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Jun 14, 2001* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search. (See NOTE below);

   (b) ☒ they raise the issue of new matter. (See NOTE below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: *Newly proposed claim 20 recites generic embodiments comprising a "signal peptide" limitation which constitutes new matter. Claims 1, 20, and 21 lack antecedent basis over "the implantation" (see "other")*

4. ☐ Applicant's reply has overcome the following rejection(s):

5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in separate, timely filed amendment cancelling the non-allowable claim(s).

6. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
Arguments directed to the newly proposed claims are moot, since they have not entered. To the extent that the arguments apply to the previously filed claims the following arguments apply: (see attached)

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):

   Claim(s) allowed: *none*

   Claim(s) objected to: *none*

   Claim(s) rejected: *1, 3-8, 11-15, and 20-31*

9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.

10. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

11. ☒ Other: *and "the coding polynucleotide"; claims 21 and 31 are rendered indefinite by "for termination...permitting the secretion".*

Attachment to Advisory Action

The arguments directed to the new matter rejection over use of the term signal peptide are not persuasive, since neither the figures (i.e. Fig. 1a and 2a) nor the specification make any mention of signal peptides or indicate that such sequences or domains are related to the instant application. However, even if there was such a description with respect to Figures 1a and 2a, this would have only provided support for the particular *species* of polynucleotides recited therein; since there are no generic descriptions of polynucleotides comrpising signal peptides in the instant application, there is no written support for generic embodiments reciting sequence encoding signal peptides. The response further contends that "Applicants have amended claims 1, 20, 21, and 31 to remove the term 'signal peptide'"; however, contrary to Applicants assertion, newly proposed claim 20 newly introduces this term, which is new matter as described.

With regard to lack of enablement, Applicants arguments fail to overcome the *prima facie* evidence against therapeutic delivery and fail to provide sufficient evidence to refute the lack of guidance or evidence of a well-established use for non-therapeutic delivery in accordance with the claimed invention. For example, regarding the correlation between *in vitro* and *in vivo* data (top, p. 8), the response recites passages from the MPEP without providing any evidence to refute the need for correlative evidence *in vitro* and *in vivo* data, *given the unpredictability and lack of success in the art as set forth in the evidence of record.* The response further provides the unsubstantiated assertion that the "the Examiner has supplied no objective evidence as to the alleged non-enablement, but simply offered a personal opinion". To the contrary, the Office has

presented ample, specific and objective grounds for lack of enablement as directed to therapeutic delivery. Further, the grounds for lack of enablement were not predicated on questions of whether an implanted cell would be capable of secreting *some level* of antibody, but rather whether the level of secretion was commensurate with a therapeutic benefit.

As alluded to above, the response fails to refute the lack of guidance or lack of evidence of a well-established use either for the claimed methods of non-therapeutic *ex vivo* cell delivery in mammals or for cell compositions comprising intended use limitations directed to such; therefore, the specification fails to provide an enabling disclosure commensurate with the scope of the claimed subject matter. Arguments directed to genetically modified cells engineered to produce and secrete factor IX, VEGF etc. are not persuasive, because the response fails to establish a nexus (with any specificity) between those results, reported in the post-filing art, and Applicants disclosure as filed. Further, the arguments directed to murine models alleged to be predictive of enablement are not persuasive, because when read in light of the specification, the claims are interpreted to read on therapeutic delivery. The claims do not refer to such models, nor does the response establish a nexus between the embodiments described in subject matter incorporated by reference on p. 8-10 and the invention *as claimed.* The response contends that "[a]s the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating" (p. 10). However, the response fails to provide any specific evidence demonstrating any correlation between the working examples and any particular therapeutic

effect, let alone a correlation that would be commensurate with the broad scope of the claimed subject matter.

The arguments directed to human testing are unclear, since lack of enablement in the instant case was never described as being predicated on human testing. The response further relies upon two selected passages from the MPEP, taken out of context, which were interpreted as suggesting the lack of requirement for correlation between *in vitro* assays or animal models and a particular therapeutic or pharmacological utility (p. 11). Importantly, the first passage is *qualified* by the statement "[I]f reasonably correlated to the particular therapeutic or pharmacological utility" (underlining added). The second passage is directed to the notion that the applicant does not have to prove that a correlation exists...as a matter of statistical certainty...[but rather]...a reasonable correlation between the activity and the asserted use". However, the response fails to provide any such evidence of a "reasonable correlation" for the reasons already set forth above.

Regarding undue experimentation (p. 11-12), the response contends that "a considerable amount of experimentation is permissible, *if is merely routine*, or if the specification in question provides a reasonable amount of guidance" (bottom of p. 11, emphasis added). That is the point. In view of the unpredictability in the art, the lack of guidance, and the fact that therapeutic delivery was not routinely achieved at the time of filing, it would require undue experimentation to enable the scope of the claimed subject matter for the reasons of record, the *specific* reasons of which were not fully addressed.

With regard to the rejections over prior art, the previous rejection are maintained in view of the response's failure to provide any new or convincing arguments to refute the specific bases for anticipation set forth in the evidence of record as directed to the invention *as claimed.* Applicants are reminded that several of the arguments in the response are directed to the newly amended claims which were not entered; therefore these arguments are moot with respect to the claims under examination.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER